

REMARKS

Claims 1-25 are pending in this application. Claims 18-21 have been withdrawn from consideration as being drawn to a non-elected invention. Claims 1, 3-14, 16-17, 22, 23, and 25 have been amended.

Applicants, by amending the claims, make no admission as to the validity of any rejection made by the Examiner against any of these claims. Applicants reserve the right to reassert the original claim scope of any claim amended herein, in a continuing application.

Claim 1 has been amended to further recite: “g) outputting a computer output of the expanded all-atom representation of the primary structure(s) obtained in step (f) that predicts at least one amino acid sequence that folds into a specified three-dimensional (3D) structure of the predetermined reference protein or peptide, and wherein the at least one amino acid sequence has a biological activity the same as a biological activity of the reference protein or peptide.” Support for amended claim 1 can be found throughout the specification and claims as originally filed, for example, see the preamble of claim 1. No new matter has been added.

Claim 23 has been amended to replace the phrase “said input means” with the phrase “the input apparatus.” Support for amended claim 23 appears throughout the specification and claims as originally filed. No new matter has been added.

Claims 8, 10, and 12 have been amended to further recite that the amino acid residues are each independently selected from the group recited. Support for amended claims 8, 10, and 12 appears throughout the specification and claims as originally filed. No new matter has been added.

Claims 1, 3-14, 16-17, 22, 23, and 25 have been amended to replace the word "said" with the word "the." Claim 4 has been amended to replace the phrase "may comprise" with "comprises." No new matter has been added.

In view of the remarks set forth below, further and favorable consideration is respectfully requested.

I. A page 2 of the Official Action, claim 24 has been rejected under 35 USC § 112, first paragraph, as failing to comply with the written description requirement.

The Examiner asserts that claim 24 includes new matter not supported by the specification or original claims. The Examiner asserts that the specification and original claims do not disclose that the dead-end elimination algorithm is not used with the claimed method.

Applicants disagree with the Examiner's position regarding the written description support in the specification, as one of ordinary skill in the art reading the specification would understand the recited method of claim 24 is inherently disclosed in the specification, for example, at page 4, lines 1-4, which discusses inadequate prior art methods including the dead-end elimination algorithm; and at page 3 of the specification which states that "*de novo* design of stable and unique proteins, remains a challenging problem."

Accordingly, the Examiner is respectfully requested to reconsider and withdraw this rejection.

II. At page 3 of the Official Action, claim 23 has been rejected under 35 USC § 112, second paragraph, as being indefinite.

The Examiner asserts that in claim 23 there is insufficient antecedent basis for the phrase "said input means" in line 12.

In view of the following, this rejection is respectfully traversed.

Claim 23 has been amended to replace the phrase "said input means" with the phrase "the input apparatus."

In view of the foregoing, it is submitted that claim 23 is clear and definite within the meaning of 35 USC §112, second paragraph. Accordingly, the Examiner is respectfully requested to withdraw this rejection.

III. At page 5 of the Official Action, claims 1-17 and 22-24 have been rejected under 35 USC § 101, as being directed to non-statutory subject matter.

The Examiner asserts that the instant claims are drawn to a process involving the judicial exception of a computational algorithm, and do not require a tangible result.

In view of the following, this rejection is respectfully traversed.

In order to advance prosecution, and without acquiescence to the rejection or disclaimer to the subject matter recited or amended, Applicants have amended claim 1 to further recite the following: "step g) outputting a computer output of the expanded all-atom representation of the primary structure(s) obtained in step (f) that predicts at least one amino acid sequence that folds into a specified three-dimensional (3D) structure of the predetermined reference protein or peptide, and wherein the at least one amino acid sequence has a biological activity the same as a biological activity of the reference protein or peptide." This additional language is recited in the preamble of claim 1 and is now

included in the description of the computer output of step g) and clearly includes a tangible result.

In view of the foregoing, Applicants submit that the presently claimed subject matter requires a tangible result and thus is directed to statutory subject matter within the meaning of 35 USC § 101. Accordingly, the Examiner is respectfully requested to withdraw this rejection.

IV. At pages 5-10 of the Official Action, claims 1-5, 9-17, 22 and 23 have been rejected under 35 USC § 103 as being unpatentable over Dahiyat et al., and further in view of Herzyk et al. Claims 6-8 have been rejected as being unpatentable over Dahiyat et al., and further in view of Herzyk et al. and further in view of Hurley et al.

The Examiner asserts that it would have been obvious to the skilled artisan to “to combine the teaching of Dahiyat et al.” The Examiner reasons that “one of ordinary skill in the art could have taken the data of Dahiyat et al. and represented that data in the teachings of Herzyk et al.” and that “one of ordinary skill in the art could have combined the elements as claimed by known methods with no change in their respective functions.”

With regard to claims 6-8, the Examiner states that neither Dahiyat et al. nor Herzyk et al. teaches that the solvent is substantially water, but that it would have been obvious to the skilled artisan “to combine the teaching of Dahiyat et al., Herzyk et al. and those of Hurley et al.” as Hurley et al. teach that “it would have been obvious to determine the structure of an amino acid in water because it would have allowed for the calculation of stability.”

In view of the following these rejections are respectfully traversed.

To establish a *prima facie* case of obviousness, the PTO must satisfy three

requirements. First, as the U.S. Supreme Court very recently held in *KSR International Co. v. Teleflex Inc. et al.*, Slip Opinion No. 04–1350, 550 U. S. ____ (April 30, 2007), “a court must ask whether the improvement is more than the predictable use of prior art elements according to their established functions. ...it [may] be necessary for a court to look to interrelated teachings of multiple patents; the effects of demands known to the design community or present in the marketplace; and the background knowledge possessed by a person having ordinary skill in the art, all in order to determine whether there was an apparent reason to combine the known elements in the fashion claimed by the patent at issue. ...it can be important to identify a reason that would have prompted a person of ordinary skill in the relevant field to combine the elements in the way the claimed new invention does... because inventions in most, if not all, instances rely upon building blocks long since uncovered, and claimed discoveries almost of necessity will be combinations of what, in some sense, is already known.” (*KSR, supra*, slip opinion at 13-15.) Second, the proposed modification of the prior art must have had a reasonable expectation of success, determined from the vantage point of the skilled artisan at the time the invention was made. *Amgen Inc. v. Chugai Pharm. Co.*, 18 USPQ2d 1016, 1023 (Fed. Cir. 1991). Lastly, the prior art references must teach or suggest all the limitations of the claims. *In re Wilson*, 165 USPQ 494, 496 (C.C.P.A. 1970).

With regard to motivation to combine references, **MPEP 2143** discusses the requirements of a *prima facie* case of obviousness. First, there must be some suggestion or motivation to combine the reference teachings or to modify the reference, and second, there must be a reasonable expectation of success. Finally, the prior art reference or references when properly combined, must teach or suggest all the claim limitations.

Regarding motivation to modify properly combined references, **MPEP 2143.01** states that a proposed modification cannot render the prior art unsatisfactory for its intended purpose. If it does, then there is no suggestion or motivation to make the proposed modification. Further, the proposed modification cannot change the principle operation of a reference.

Regarding *teaching away*, **MPEP 2141.02** states that prior art must be considered in its entirety, including disclosures that *teach away* from the claims. See also **MPEP 2145(X)(D)**. The Federal Circuit in *Takeda v. Alphapharm* found that the prior art taught away from the closest compound because the prior art in fact disclosed a broad selection of compounds where the closest prior art compound exhibited negative properties that would have led the skilled artisan away from that compound.

The Examiner, in the sentence bridging pages 8 and 9 of the Official Action, asserts that the Board Of Patent Appeals and Interferences applies *KSR* in *Ex parte Smith* (decision dated June 25, 2007) and thereby “forecloses the argument that a specific teaching, suggestion, or motivation is required to support a finding of obviousness.” However, the Board decision in *Ex parte Smith* is largely modified, if not negated, three days later by the Court of Appeals for the Federal Circuit in *Takeda Chemical Industries v. Alphapharm*, 492 F.3d 1350, 84 USPQ2d 1197 (June 28, 2007).

In *Takeda*, the Federal Circuit validated the continued use of the teaching, suggestion, motivation (TSM) test for obviousness after *KSR*, in particular for unpredictable arts such as in pharmaceuticals and biotechnology. The Federal Circuit rejected Alphapharm's argument that the prior art would have led one of ordinary skill in the art to select compound b as a lead compound most promising to modify in order to improve its

antidiabetic activity and thus potentially arrive at the claimed pioglitazone. The district court considered three references in reaching its determination, namely Takeda's '200 patent; Sodha II; and Takeda's '779 patent. The district court found that Sodha II taught away from compound b and that any suggestion in the '779 patent to select compound b was essentially negated by the disclosure of Sodha II in view of the more exhaustive and reliable scientific analysis presented by Sodha II and the teaching away. Accordingly, the Federal Circuit accorded more weight to the Sodha II reference. In addition, the Court also rejected the Appellant's "obvious to try" argument, as the Appellant failed to demonstrate that one of ordinary skill would have chosen the prior art compound to modify from the millions of possibilities. *Id.* at 1360.

Furthermore, subsequent to the issuance of the holding in *Ex parte Smith*, the Examiner's attention is directed to more recent Board decisions that have verified the continued validity of applying the teaching, suggestion, and motivation test for obviousness. For example, in *Ex parte Whalen* (Appeal 2007-4423, precedential opinion issued July 23, 2008) the Board stated, at pages 15-16, that the Court in *KSR* did not discard the TSM test, and then the Board applied the test to overturn the Examiner's obviousness rejections (emphasis added).

The U.S. Supreme Court recently held that rigid and mandatory application of the "teaching-suggestion-motivation," or TSM, test is incompatible with its precedents. *KSR Int'l Co. v. Teleflex Inc.*, 127 S.Ct. 1727, 1741 (2007). **The Court did not, however, discard the TSM test completely**; it noted that its precedents show that an invention "composed of several elements is not proved obvious merely by demonstrating that each of its elements was, independently, known in the prior art." *Id.*

The Court held that ***the TSM test must be applied flexibly, and take into account a number of factors "in order to determine whether there was an apparent reason to combine the known elements in the fashion***

claimed.” *Id.* at 1740-41. Despite this flexibility, however, the Court stated that “it can be important to identify a reason that would have prompted a person of ordinary skill in the relevant field to combine the [prior art] elements in the way the claimed new invention does.” *Id.* ***“To facilitate review, this analysis should be made explicit.”*** *Id.* 15

The obviousness rationale addressed in *KSR* was premised on combining elements known in the prior art. *Id.* at 1738-39. A parallel analysis applies, however, to a rejection premised on the obviousness of modifying a known composition to change its properties.

The *KSR* Court noted that ***obviousness cannot be proven merely by showing that the elements of a claimed device were known in the prior art; it must be shown that those of ordinary skill in the art would have had some “apparent reason to combine the known elements in the fashion claimed.”*** *Id.* at 1741.

In the same way, when the prior art teaches away from the claimed solution as presented here (FF12, FF20, FF22 and FF 24), ***obviousness cannot be proven merely by showing that a known composition could have been modified by routine experimentation or solely on the expectation of success; it must be shown that those of ordinary skill in the art would have had some apparent reason to modify the known composition in a way that would result in the claimed composition.***

The Examiner has not persuasively explained why a person of ordinary skill in the art would have had a reason to modify the compositions taught by Evans, Greff '767, or Taki in a way that would result in the compositions defined by the claims on appeal. Therefore, the Examiner has not made out a prima facie case of obviousness under 35 U.S.C. § 103. We reverse the rejections of claims 1-13 and 15-17 as obvious in view of Evans; the rejection of claims 1-17 as obvious in view of Greff '767; and the rejection of claims 1-6, 9, 10, and 14-17 as anticipated by or obvious in view of Taki.

It is submitted that a *prima facie* case of obviousness has not been established.

In the amendment filed responsive to the first Official Action, claim 1 was amended to recite that a single sphere is used to represent the backbone of each amino acid and one to three additional spheres are used to represent the amino acid's side chain. To support the rejections in the present office action, the Examiner asserts the following

(emphasis added):

One of ordinary skill in the art **could have taken** the the data of Dahiyat et al. and represented that data in the teachings of Herzyk et al. One of ordinary skill in the art **could have combined** the elements as claimed by known methods with no change in their respective functions.

Applicants submit that the Examiner has ***not explicitly provided sufficient reasoning*** that would have prompted a person of ordinary skill in the relevant field to combine the prior art elements in the way the claimed new subject matter does. As noted above by the Board in *Ex parte Whalen*, and as supported by the Court in *KSR*, “***obviousness cannot be proven merely by showing that a known composition COULD have been modified.***” The Examiner’s generalized statements that one “could have” used and combined the prior art elements provides insufficient reasoning for what would have prompted one of ordinary skill in the art to combine the noted elements in the particular way claimed by Applicants. Accordingly, the Examiner’s rejections and underlying reasoning provide insufficient evidentiary support for showing a case of *prima facie* obviousness.

Furthermore, a *prima facie* case of obviousness has also not been shown for the reason that the combination of cited documents does not teach or suggest the presently claimed invention.

For example, the step of converting the low resolution representation to the high representation is recited in part (f) of claim 1. The Examiner alleges (see page 7 of the Official Action starting from line 6 from the bottom) that this step is taught in Dahiyat and refers to page 899 of Dahiyat for support. Though the Examiner does not specifically point out where this teaching is recited on page 899, it appears that he is referring to the

sentence bridging pages 889-890. This sentence relates to the QSAR analysis of the results Dahiyat obtained with their method. However, Applicants submit that this sentence has nothing to do with replacing a low resolution representation with a high resolution representation as asserted in the rejection. Furthermore, this sentence relates to the QSAR analysis of the results they obtained with their method, and is not part of their method for obtaining the results. Moreover, this sentence is written in the negative ("simpler structure measures were not deemed significant by the QSAR analysis"), and thus it is not clear how this would affirmatively teach or suggest the claimed method step. Therefore, the Examiner's assertion that step (f) of Claim 1 is taught in Dahiyat, is completely unsubstantiated.

Also, the Examiner points out that the method of the Dahiyat et al. teaches that "following DEE optimization, a rank-ordered list of sequences is generated by Monte Carlo search in the neighborhood of the DEE solution...random position are changed to other rotamers, and the new energy is calculated." The Examiner asserts that this corresponds to step (e) of claim 1.

However, although the Dahiyat et al. publication uses an "all atom" representation of the amino acids, the Dahiyat et al. publication **reduces** computer time by implementing a search method based upon the **dead-end elimination theorem** (see abstract of Dahiyat et al.). Thus, Dahiyat et al. reduces computer time by a method that is **completely different** from the presently claimed method. In contrast to Dahiyat et al., the present application uses a low resolution representation of the amino acids throughout the computations and, after identification of the final structure, the final structure is expanded to the "all-atom" representation. Replacing the all atom representation of the Dahiyat et al. publication with

the reduced representation of the Herzyk et al. publication would **not** produce the method of the present invention ***because the present search method does not utilize the dead-end elimination algorithm required by Dahiyat et al.*** Moreover, Dahiyat et al. also teaches away from the present claims since Dahiyat et al. cannot have a step of expanding a low resolution representation to a high resolution representation, because Dahiyat et al. uses the high resolution representation from the beginning, and never uses a low resolution representation.

It is not possible to predict from the teachings of the Herzyk et al. publication whether or not, in any application of the described reduced amino acid representation, the most satisfactory solutions are eliminated. The present inventors have surprisingly found that using a reduced representation of the amino acids in their presently claimed method does, in fact, yield a satisfactory ***high resolution*** protein structure. This could not have been predicted from the teachings of the Herzyk et al. publication. Quite to the contrary, the Herzyk et al. publication states at the end of the abstract: "The new representation is adequate for describing the 'low-resolution' features of protein structure such as the general fold and the positions of secondary structure elements. It can also provide an initial structure for more detailed refinement with the full all-atom representation." The skilled artisan reading the Herzyk et al. publication would understand that using the described manner of representing amino acids in the method of Dahiyat et al. would yield ***only a low resolution structure***, and that additional work, i.e., full all-atom representation, would be required to produce a high resolution structure. The present inventors have found, quite surprisingly, that the presently claimed method using a reduced representation of the amino acids, yields a high resolution structure without the need for any further refinement.

Accordingly, the Examiner is respectfully requested to reconsider and withdraw the obviousness rejection over Dahiyat et al. in view of Herzyk et al.

Claims 6-8 have been rejected as being unpatentable over Dahiyat et al. in view of Herzyk et al. and further in view of Hurley et al. Hurley et al. is recited by the Examiner for further teaching design and structural analysis of alternate hydrophobic core packing arrangements in water in bacteriophage T4 lysozyme. Applicants traverse the rejection for the following reasons. Applicants incorporate by reference herein the above arguments for Dahiyat et al. in view of Herzyk et al., and apply them against the rejection of claim 6-8 over Dahiyat et al. in view of Herzyk et al. and further in view of Hurley et al. Applicants submit that Hurley et al. does not cure the deficiencies of Dahiyat et al. and Herzyk et al. taken either alone or in combination.

Accordingly, the Examiner is respectfully requested to reconsider and withdraw the obviousness rejection over Dahiyat et al. in view of Herzyk et al. and further in view of Hurley et al.

In view of the foregoing, it is submitted that nothing in any of Dahiyat et al. and Herzyk et al., as well as Dahiyat et al., Herzyk et al. and Hurley et al., taken alone or together, renders the claimed subject matter obvious within the meaning of 35 USC §103. Accordingly, the Examiner is respectfully requested to withdraw these rejections.

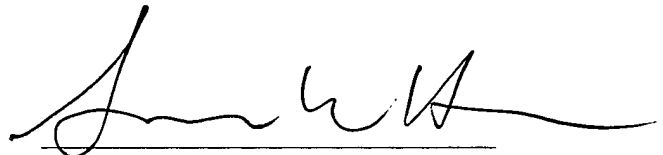
Conclusion

In view of the foregoing, Applicants submit that the application is in condition for immediate allowance. Early notice to that effect is earnestly solicited. The Examiner is invited to contact the undersigned attorney if it is believed that such contact will expedite the prosecution of the application.

In the event this paper is not timely filed, Applicants petition for an appropriate extension of time. Please charge any fee deficiency or credit any overpayment to Deposit Account No. 14-0112.

Respectfully submitted,

THE NATH LAW GROUP

A handwritten signature in black ink, appearing to read 'Gary M. Nath', written over a horizontal line.

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